REMARKS

Claims 1-5, 7-10, 12-15, 17, 19-20, 25, 26, 28, 30-32, 34-42, 44-52 and 54–72 are pending in this application in view of Applicant's Amendments filed March 26, 2007, August 17, 2007 and October 18, 2007. Claims 38-42 and 44-52 are withdrawn from consideration by the Examiner as allegedly being drawn to nonelected subject matter. By entry of this Amendment, Applicant hereby cancels claims 56-63, 66, 69 and 70 without prejudice. Applicant further hereby amends claims 1-5, 7, 8, 10, 12-15, 17, 19, 64, 67, 68, 71 and 72. New claims 73-78 are added.

Support for these amendments can be found throughout the specification and is discussed below.

Accordingly, claims 1-5, 7-10, 12-15, 17, 19-20, 25, 26, 28, 30-32, 34-42, 44-52 and 54, 55, 64, 65, 67, 68 and 71–78 shall be pending upon entry of this Amendment.

No new matter is being added by this Amendment.

Newly added claims 73-78 are drawn to a method of classifying DZIP1 gene expression in a human test subject. Support for the newly added claims can be found, for example, on page 74 of the instant specification, which states:

> Classification or class prediction of a test sample of an individual so as to determine whether said individual has type 2 diabetes or does not have type 2 diabetes can be done using the differentially expressed genes as shown in Table 3G as the predictor genes in combination with well known statistical algorithms as would be understood by a person skilled in the art and described herein. Commercially available programs such as those provided by Silicon Genetics (e.g. GeneSpring™) for Class Predication are also available

See Example 16, page 74, lines 1-6, of the instant specification.

The claim objections are overcome

The Office action objects to claims 34, 35 and 36 under 37 C.F.R. 1.75(c) as being in improper form as allegedly failing to form a multiple dependent claim that depends from previous claims in the alternative. Applicant respectfully disagrees with the objection and traverses as follows.

In this regard, the MPEP requires that "[a] multiple dependent claim may refer in the alternative to only ***one set*** of claims. A claim such as "A device as in claims 1, 2, 3, or 4, made by a process of claims 5, 6, 7, or 8" is improper. 35 U.S.C. 112 allows reference to only a particular claim." See MPEP § 608.01 (emphasis added).

Applicant respectfully asserts that claims 34, 35 and 36 conform with this rule because they each refer only to ***one set*** of claims. To clarify, each of claims 34, 35 and 36 depend from claim 32, which, in turn, is dependent on claim 30, which, in turn, is dependent on the claim set 1-4 and 12-15. While claims 34, 35 and 36 additionally recite the markers of claims 2, 3 and 4, respectively, claims 2, 3 and 4 are already inclusive of the claim set of claim 30, i.e., included in the claim set 1-4 and 12-15.

Accordingly, claims 34, 35 and 36 each ultimately depend from only one set of claims, i.e., claims 1-4 and 12-15, in accordance with the above requirements..

Reconsideration and examination of these claims is respectfully requested.

The rejections under 35 U.S.C. § 112, 2nd paragraph (indefiniteness) are overcome

Claims 13-15, 17, 19, 20, 25-26, 28, 30-32, 37, 56-63 and 66-72 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

As an initial matter, by this Amendment, Applicant has cancelled claims 56-63 and 66 without prejudice and solely in the interest of advancing prosecution, rendering the rejections, to the extent they apply to those claims, moot.

As to the remaining rejected claims, Applicant respectfully disagrees with the rejections and traverses as follows.

As to claim 13, the Office action contends the claim is indefinite because the preamble and the final process step of the claims recite testing expression in "human test subjects" (plural) yet the method steps refer only to a "test subject" singular.

Without wishing to concede the rejection, Applicant has amended claim 13 to remove the recitation of the phrase "human test subjects."

As to claims 14 and 15, the Office action states the claims are indefinite because the preamble and the method steps of the claims refer to a human test subject (singular) while the final process step refers to the blood of "human test subjects" (plural), consequently rendering the claim confusing.

Without wishing to concede the rejection, Applicant has amended claims 14 and 15 to remove the recitation of the phrase "human test subjects."

Applicant has further removed the dependency of claims 67-72 from newly cancelled claim 66 without prejudice, thus rendering the instant rejection of claims 67-72 moot.

In light of the above remarks and claim amendments, Applicant respectfully requests reconsideration and withdrawal of the Section 112, 2nd paragraph rejections.

The rejections under 35 U.S.C. § 112, 1st paragraph (enablement) are overcome

Claims 12-15, 17, 19-20, 25-26, 28, 30-32, 37 and 60-72 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.

Applicant respectfully traverses. Applicant disagrees with the rejection's assertion that the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art. The enablement rejection will be addressed only to the extent as they apply to the currently pending claims. Applicant has canceled claims 60-63, 66 and 69-70, solely in the interest of advancing prosecution, rendering their rejection moot.

Independent claims 12-15, and their associated dependent claims, as newly amended, are drawn to a method of detecting a difference in expression of a gene in a human test subject suspected of having Type II diabetes as compared with healthy human control subjects. Applicant has narrowed the scope of the control subjects by reciting that they be healthy human control subjects and have further characterized the difference in gene expression be statistically significant where $p < 0.05$.

Applicant respectfully disagrees with the Office action's contention on page 14 that the "test genes are entirely unidentified," because test genes, in fact, are identified throughout the specification. For instance, Example 6 exemplifies the differential expression of insulin in diabetic patients versus healthy controls, Fig. 4 shows differential expression of ZFP in diabetic patients versus healthy controls, and Example 16, along with corresponding Table 3G,

exemplifies 915 genes differentially expressed genes with a p value of <0.05 as between Type II diabetes and nondiabetic controls. Thus, Applicant has identified and exemplified in the specification the differential expression of test genes in whole blood of patients having diabetes relative to controls. Applicant knows of no such previously published data regarding the pivotal and fundamental claimed invention.

Independent claims 64-72 are drawn to a method of identifying a human test subject as being a candidate for having Type II diabetes, comprising determining the level of RNA encoded by DZIP1 in a blood sample obtained from said human and comparing the level of corresponding RNA from blood samples from healthy control subjects, wherein said comparison is indicative of Type II diabetes in said human test subject. Applicant has newly amended the claims such that diabetes is limited to Type II diabetes, and narrowed the scope of the control subjects by reciting that they be healthy control subjects, and have further characterized the difference in gene expression be statistically significant where $p< 0.05$.

Applicant disagrees with the contention that a comparison with as few as two control subjects is insufficient to conclude that all diabetes is detected. The claims as newly amended are limited to Type II diabetes. Further the newly added limitation that $p< 0.05$ clearly removes the possibility of having only 2 controls.

The Office action further states on page 13 that the claims require the knowledge of a relationship between an indication of diabetes and the expression of two or more genes that are expressed in a blood and non-blood tissue of a subject. Applicant respectfully submits such a reliable associate is indeed presented in the specification.

For example, with regard to DZIP1, a reliable association between comparing DZIP1 expression and the indication that diabetes is present in a human is demonstrated in the

specification. In particular, Example 16 discloses that the identification of the DZIP1gene as a differentially expressed gene in blood samples from individuals having diabetes as compared with the expression of the gene in healthy individuals. Specifically, Example 16 discloses:

> Total mRNA from a drop of peripheral whole blood taken from each patient was isolated using TRIzol^{RTM} reagent (GIBCO) and fluorescently labelled probes for each blood sample were generated as described above. Each probe was denatured and hybridized to a 15K Chondrogene Microarray Chip (ChondroChip™) as described herein. Identification of genes differentially expressed in blood samples from patients with type 2 diabetes as compared to healthy patients was determined by statistical analysis using the Wilcox Mann Whitney rank sum test (Glantz SA., Primer of Biostatistics., 5th ed., New York, USA: McGraw-Hill Medical Publishing Division, 2002).
>
> Figure 14 shows a diagrammatic representation of gene expression profiles of blood samples from individuals who were identified as having type 2 diabetes as described herein as compared with gene expression profiles from normal and non-type 2 diabetes individuals. Expression profiles were generated using GeneSpring™ software analysis as described herein. Each column represents the hybridization pattern resulting from a single individual. Normal individuals have no known medical conditions and were not taking any known medication. Non-type 2 diabetes individuals presented without type 2 diabetes, but may have presented with other medical conditions and may be under various treatment regimes. Hybridizations to create said gene expression profiles were done using the ChondroChip™. A dendogram analysis is shown above. Samples are clustered and marked as representing patients who have type 2 diabetes, are normal or do not have type 2 diabetes. The "*" indicates those patients who abnormally clustered despite actual presentation. The number of hybridizations profiles determined for type 2 diabetes, non-type 2 diabetes and normal individuals are shown. 915 were identified as being differentially expressed with a p value of < 0.05 as between the type 2 diabetes patients and the combination of normal and non type 2 diabetes individuals is noted. The identity of the differentially expressed genes is shown in Table 3G. (see page 73 of the application)

Further, Table 3G, entitled "Genes Corresponding To Differentially Expressed Genes in Figure 14 - Diabetes", lists zinc-finger protein DZIP1 as being differentially expressed with a p value = 0.013668331, and locates it on GeneSpot 10110 of the ChondroChip^{TM}. In addition, Fig. 4 provides quantitative data showing the relative levels of transcripts corresponding to the insulin gene (INS), zinc-finger protein gene, and a house-keeping gene (GADH) detected from blood obtained from a normal subject, late-onset Type II diabetic subject and an asymptomatic diabetic

subject. Fig. 5 shows standardized levels of insulin and zinc-finger protein gene expressed in a drop of blood from normal versus late onset Type II diabetic subjects. Thus, Figs. 4 and 5 provide the relative magnitude and direction of the differential expression of the insulin and ZFP genes.

Applicant respectfully submits, that based on the above expression data and statistical analyses of insulin and DZIP1 expression in blood samples of diabetes patients and of normal individuals, the specification supports the instantly claimed methods.

The Office action also states on page 19 that no replicate data is found in the instant specification. Applicant respectfully disagrees, and submits that the multiple subjects tested per positive and negative control groups in the reduction to practice of the instant claims inherently constitutes a replication, clearly reliably satisfying the language of claim 58, namely: "detecting a difference in expression of a DZIP1 gene in a human test subject suspected of having Type II diabetes as compared with healthy human control subjects."

The Office action further states that the instant claims require the knowledge of whether DZIP1 would be expressed in the blood of patients having other diseases which were not tested and whether this expression would be different from the levels of healthy controls. However, these claims are not meant to function as a method which would necessarily be a test to be relied on for the detection of diabetes to the exclusion of any and all other diseases, but rather is one method available to be used in conjunction with other methods to provide a diagnosis of diabetes Type II. Applicant notes that even the much litigated patented method claims of Metabolite Laboratories, Inc.'s U.S. Patent No. 4,940,658, ('658), include method steps which can be used to indicate a disease or disorder other than the disease/disorder recited. For example, Claim 13 of '658 is drawn to a method for detecting a deficiency of cobalamin or folate in warm-blooded

animals by assaying a body fluid for an elevated level of total homocysteine, and is thus used as a method to detect vitamin deficiency. However, it was well known in the medical community before the filing of '658, that the assay for elevated homocysteine levels could signal an increased risk of heart disease. Despite much scrutiny for other reasons, claim 13 of '658 has not been invalidated as a result of other previously known use(s) of its claimed assay to provide a correlation to a second disease or disorder not recited in its claim 13.

Regarding the Office action's contention that in order to practice the claimed invention one would have to undertake an extensive amount of experimentation. Applicant respectfully submits that a considerable amount of experimentation is permissible to practice the claimed invention, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Applicant respectfully submits that by disclosing which genes are differentially expressed in blood of samples from individuals with diabetes versus negative controls, Applicant has provided those of skill in the art one method, albeit not necessarily an exclusive method, to aid in detecting/screening Type II diabetes. It will be appreciated that as long as the specification discloses ***at least one method*** for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. See In re Fisher, 427 F.2d 833, 839 (CCPA 1970). Failure to disclose other methods by which the claimed invention may be made does ***not*** render a claim invalid under Section 112. See Spectra-Physics, Inc. v. Coherent, Inc. 827 F.2d 1524, 1533 (Fed. Cir.), *cert. Denied*, 484 U.S. 954 (1987). Moreover, the fact that Applicant has exemplified specific genes which are differentially expressed with a p value of less than 0.05 from then thousands and with values that are often much lower than 0.05,

is the nexus of the invention. Methods and protocols for applying differentially expressed genes to indicate the presence of a disease or condition, ***regardless of direction of change of expression***, are well established in the art and disclosed herein. For example, Slonin DK, Nature Genetics Supplement, Vol. 32, 502-8 (2002), which is incorporated by reference in the instant specification at paragraph 133 of the published application (2004/0265869), states that "***[t]he most basic question one can ask in a transcriptional profiling experiment is which genes' expression levels changed significantly***." Applicant respectfully submits that Table 3G, in fact, provides which genes' expression levels changed significantly; and thus, the specification comports with the methods and protocols generally accepted in the art.

In *In re Wands*, the court further stated that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. 'The key word is 'undue' not 'experimentation' (citing *In re Angstadt*, 537 F. 2d 498 at 504, 190 U.S.P.Q. 214 at 219 (C.C.P.A. 1976)). The Court also stated that "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (citing In re Jackson, 217 U.S.P.Q. 804 at 807 (Bd. App. 1982)).

In summary, Applicant believes there is sufficient guidance provided by the specification and that the art is sufficiently predictable such that the amount of experimentation to perform the subject matter within the instant claims is not undue.

In view of the remarks and claim amendments, Applicant respectfully requests reconsideration and withdrawal of the rejection of the instant claims.

The rejections under 35 U.S.C. § 103 are overcome

Claims 1, 2, 5, 7, 8, 9, 12, 13, 19, 20, 25, 26, 30, 31, 32, 37, 54, 55, 56, 57, 60 and 61 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable obvious over Page *et al.* (1997, Biochemical and Biophysical Research Communications 232:49-53) (herein as "PAGE") in view of Sharma *et al.* (WO 98/49342) (herein as "SHARMA"). Applicant has cancelled claims 56, 57, 60 and 61 without prejudice, rendering the rejection moot as it pertains to those claims.

The Office action also rejects claims 3, 4, 5, 7, 8, 9, 14, 15, 19, 20, 25, 26, 28, 30, 31, 32, 37, 54, 55, 58, 59, 62 and 63 under 35 U.S.C. § 103(a) as allegedly being unpatentable over PAGE in view of SHARMA, and in further view of Ralph *et al.* (U.S. Patent No. 6,190,857) (herein as "RALPH") (or the corresponding PCT published application, WO 98/24935). Applicant has cancelled claims 58, 59, 62 and 63 without prejudice, rendering the rejection moot as it pertains to those claims.

Applicant respectfully disagrees with each of the above remaining rejections and traverses as follows.

As an initial matter, it is noted that Graham v. John Deere Co., 338 U.S. 1, 148 USPQ 459 (1966), was recently reaffirmed by KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727, 82 USPQ2d 1385 (2007) as providing the correct analytical framework for determining obviousness. Under Graham, obviousness is a question of law based on underlying factual inquires that address (1) the scope and content of the prior art, (2) the differences between the claimed invention and the prior art, and (3) the level of ordinary skill in the pertinent art. Evidence of secondary factors (e.g., commercial success, long-felt but unmet need, and unexpected results) are also given weight in the analysis. Moreover, to establish a *prima facie*

obviousness rejection of a claimed invention, ***all*** the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Additionally, any determination of obviousness also requires a clearly articulated rationale on which to properly base the Section 103 rejection, such as, for example, some teaching , suggestion, or motivation in the prior art that would have led the skilled artisan to modify or combine prior art references to arrive at a claimed invention. See MPEP § 2143.

The Office action alleges that for each of the above rejections, the combination of references is proper because their exists some teaching, suggestion, or motivation in the prior art that would have led the skilled artisan to modify or combine cited prior art to arrive at the claimed invention and that the combination of references teaches all of the required claim elements.

Under Graham, when the presently claimed invention is evaluated in view of the scope and content of the prior art and the level of ordinary skill in the art, it is readily apparent that the differences between the claimed invention and the prior art are such that the present invention would ***not*** have been obvious. ***None*** of the cited references, either alone or in combination, teach or fairly suggest each and every element required by the claims. Moreover, there would have been no motivation to combine any of the references because their combination, in fact, teaches away from the invention, and thus, no reasonable expectation of success would have been present.

Turning first to the claimed invention, independent claims 1-4 are drawn to a method of ***identifying markers useful for detecting diabetes***.

In claims 1 and 2, the method further includes the steps of ***detecting an RNA*** in a blood sample from a subject with diabetes wherein the blood has not been fractionated into cell types

and wherein the RNA is encoded or corresponds to a gene that is expressed both in the blood and in a non-blood tissue of a subject not having diabetes. The detection is performed using an oligonucleotide of a ***predetermined sequence*** that is specific for the RNA or a cDNA complementary to the RNA. The method then includes the step of quantifying a level of expression of the RNA and then determining a difference between the level of expression of the RNA from the subject with diabetes to the expression level of the corresponding RNA from corresponding blood samples from control subjects, thereby identifying the gene which encodes the RNA as a marker useful for detecting diabetes.

In claims 3 and 4, the method further includes the steps of ***producing amplification products an RNA*** of a blood sample from a subject with diabetes wherein the blood has not been fractionated into cell types and wherein the RNA is encoded or corresponds to a gene that is expressed both in the blood and in a non-blood tissue of a subject not having diabetes. The detection is performed using an oligonucleotide of a ***predetermined sequence*** that is specific for the RNA or a cDNA complementary to the RNA. The method then includes the step of quantifying a level of amplification products and then determining a difference between the level of amplification products from the subject with diabetes to a quantified level of amplification products obtained from corresponding blood samples from control subjects, thereby identifying the gene which encodes the RNA as a marker useful for detecting diabetes.

Further, independent claims 12-15 are drawn to a method of detecting a difference in expression of genes in a human test subject ***suspected of having diabetes*** as compared with ***healthy*** human control subjects.

In claims 12 and 13, the method further includes the steps of ***detecting an RNA*** in a blood sample from the human test subject wherein the blood has not been fractionated into cell

types and wherein the RNA corresponds to the gene, which is expressed in blood and in non-blood tissue of a subject other than the test subject. The detection is performed using an oligonucleotide of a ***predetermined sequence*** that is specific for the RNA or a cDNA complementary to the RNA. The method then includes the step of quantifying a level of expression of the RNA and then determining a ***statistically significant*** difference ***where $p<0.05$*** between the level of expression of the RNA from the subject with diabetes to the expression level of the corresponding RNA from corresponding blood samples from the control subjects, thereby detecting a difference in expression of the gene in the human test subject versus the human control subjects.

In claims 14 and 15, the method further includes the steps of ***producing amplification products from RNA*** of a blood sample from the human test subject wherein the blood has not been fractionated into cell types and wherein the RNA corresponds to the gene, which is expressed in blood and in non-blood tissue of a subject other than the test subject. The method then includes the step of quantifying a level of the amplification product and then determining a ***statistically significant*** difference ***where $p<0.05$*** between the level amplification product of the test subject with a quantified level of amplification product obtained from corresponding blood samples from control subjects, thereby detecting a difference in expression of the gene in the human test subject versus the human control subjects.

Turning now to the references, PAGE relates to a study reporting on the use of differential display to identify eight candidate differentially expressed kidney genes during the development of diabetes in model rats. See page 49, left column, of PAGE. More in particular, PAGE describes having used differential display based on total RNA isolated from kidneys of diabetic rats and healthy rat controls to identify those genes which were differentially expressed

under a variety of conditions and disease stages. See page 50, right column, of PAGE. Thus, PAGE concerns the identification of diabetes-related markers that are expressed in the kidney.

By contrast, the presently claimed invention has nothing at all to do with the identification of diabetes-related markers that are expressed in kidney tissue. Instead, as presently claimed, the invention is directed to methods of ***identifying diabetes markers that are expressed in whole blood*** or to methods for detecting differentially expressed genes ***in whole blood of subjects suspected of having diabetes***. PAGE plainly does not at any point contemplate or consider the identification of useful diabetes-related markers directly from whole blood, but rather is focused on investigating differential gene expression directly in a kidney. Indeed, the Office action states that PAGE does "not teach a method wherein the total RNA in a blood sample is tested." See page 5, Office action. Thus, PAGE alone fails to teach or suggest all of the elements of the claims.

Turning to SHARMA, it is respectfully submitted that the Office action incorrectly determines that PAGE, when combined with SHARMA, would have rendered the present invention obvious. It is respectfully submitted that the combination of PAGE and SHARMA would not have taught all of the elements of the claims, nor would a skilled artisan have been motivated to combine the references to achieve the present invention with any reasonable expectation of success for at least the reasons that follow.

SHARMA relates to a method of diagnosis involving the detection of differential expression of various genes whose expression are linked to a disease. See page 2. More specifically, SHARMA relates to a method involving determining a characteristic gene expression fingerprint for a disease condition based on a number of specific probes, which is purported to serve as a set of markers for the disease of interest. The fingerprint is then

compared against RNA samples isolated from a subject under study to determine whether the subject has the disease of interest. See page 3.

Unlike all of the claims of the present invention, SHARMA does not at any point teach or suggest or contemplate looking in whole blood to specifically look for markers or differentially expressed genes of diabetes. In fact, SHARMA does not teach or exemplify at any point detecting even a single discrete differentially expressed gene or marker for even a single mammalian disease, either in whole blood or from any other bodily location. Instead, SHARMA's sole working example of identifying disease-related markers relates to the diagnosis of a disease in the ***plant,*** *Arabidopsis*. See Example 4. This example involves the development of a gene expression fingerprint for a sample of *Arabidopsis* followed by probing the expression pattern of test *Arabidopsis* samples with the expression fingerprint to distinguish between healthy and diseased samples. See pages 33-34 and the results of Figure 1. There is no express specific teaching anywhere in SHARMA of identifying markers from blood or any other source that can be used to detect diabetes. Thus, like PAGE, SHARMA fails to teach or suggest all of the elements of the claims. Moreover, the combination of PAGE and SHARMA—assuming *arguendo* that there was a motivation to combine the references—still do not teach or suggest all of the elements of the claims.

Applicant further respectfully disagrees with the assertion made in the Office action that SHARMA would have provided the skilled artisan sufficient ***motivation*** to be combined with PAGE, and that such combination renders the invention obvious. More in particular, the Office action contends that a *prima facie* case of obviousness can be made because the ordinary skilled artisan would have been motivated to modify PAGE "to have additionally tested the blood of the subjects having diabetes with control samples" on the basis that SHARMA suggests, according

to the Office action, "that disease exerts a global effect on individuals and that this effect can be measured by gene expression in the blood." Applicant respectfully disagrees with this conclusion.

Again, Applicant reiterates that SHARMA does not provide exemplification of this express teaching. SHARMA fails to ***teach that diabetes is a disease which can be identified using markers that are differentially expressed in blood***, as required by the instant claims. Moreover, SHARMA does not teach or exemplify methods of detecting differential expression in blood of RNA encoded by even a single discrete mammalian gene for even single disease. Instead, SHARMA's sole working example of identifying disease markers involves plants. ***SHARMA's mere suggestion, as recited above, that any disease can be detected by examining its effects on gene expression in the blood, particularly in view of the Office action's admission that the pertinent art is highly unpredictable (page 18 of the Office action), would not have been enough to motivate the skilled artisan to take PAGE beyond its teachings to reach the present invention.*** Indeed, the Office action even states that "establishing that a particular marker is differentially expressed in a manner reliable enough to use the marker to indicate the presence of disease in a test subject is a highly unpredictable endeavor." See page 18 of the Office action. Given the above, Applicant respectfully submits that SHARMA does not provide the requisite motivation to modify PAGE reach the presently claimed invention.

While the caselaw makes it clear that some explicit teaching, suggestion, or motivation is not absolutely required to combine references, a determination of obviousness must be made based on what a person of ordinary skill in the pertinent art would have known at the time of filing based on the Graham inquiries concerning the scope and content of the prior art, the differences between the claimed invention and the art, and the level of ordinary skill in the art.

Moreover, any conclusion of obviousness requires some clearly articulated justification to combine the references, such as a reasonable expectation of success, which as with a motivation to combine, is completely lacking here.

In support, the Office action, as noted above, admits that the pertinent art is highly unpredictable. Moreover, SHARMA's mere suggestion that its method can be applied to any disease, while exemplifying its method solely in plants, is not enough to overcome the unpredictability hurdle. These facts, combined with the fact that SHARMA did not identify any single distinct marker in blood useful for detecting diabetes, or any other disease for that matter, is evidence that the proposed combination of cited references would not have predicted the presently claimed invention with any reasonable expectation of success. Neither does such predictablity or reasonable expectation of success come from PAGE. PAGE's teaching of 8 distinct genes that were differentially expressed in rat kidney provides no teaching whatsoever that blood could be used as a source of markers useful for detecting diabetes. Moreover, it is not even clear that PAGE's 8 genes are even expressed in blood or that their expression is instead tied to age (i.e., compared rats were 6 and 36 weeks of age) rather than diabetes. Because the differences between the actual teachings of both PAGE and SHARMA and the presently claimed invention are vastly different, one of ordinary skill in the art at the time of the invention would ***not*** have been able to have practiced the claimed invention with any reasonable expectation of success or predictability.

Turning now to the combination of PAGE, SHARMA and RALPH, this combination, too, fails to render the instantly claimed invention obvious. As noted already, the Office action rejects claims 3, 4, 5, 7, 8, 9, 14, 15, 19, 20, 25, 26, 28, 30, 31, 32, 37, 54, 55, 58, 59, 62 and 63 as being obvious over PAGE and SHARMA and in further view of RALPH. Applicant

respectfully traverses this rejection.

For at least the reasons already stated above, the combination of PAGE and SHARMA would not have rendered the instantly claimed invention obvious. Applicant respectfully submits that RALPH does not correct for the deficiencies in PAGE, SHARMA or their combination.

RALPH relates to a method utilizing differential expression techniques to identify cancer markers expressed by circulating leukocytes which are expressed as part of an immune response to the presence of the cancer but are not direct products of the cancer itself (see column 4-5, e.g., lines 27-31 of column 5). More in particular, RALPH relates to the detection of certain interleukens (e.g., IL-8 and IL-10 products) in the blood produced by circulating cells of the immune system, in combination with certain known markers, to detect prostate cancer. See column 5.

As noted above, the rejected claims are directed to methods of identifying diabetes markers that are expressed in whole blood samples (e.g., claims 3 and 4) or to methods for detecting differentially expressed diabetes markers in whole blood samples of subjects suspected of having diabetes (e.g., claims 14 and 15). ***The methods require the use of sequence specific oligonucleotide primers in order to obtain measurable amplification products of target biomarker genes of interest, e.g., those genes of Table 3G.***

Applicant respectfully submits that the recited steps of each of the rejected claims are drawn to an entirely different set of method steps than the teachings of RALPH. More in particular, the instantly rejected claims are essentially drawn to methods of detecting biomarker genes directly in whole blood samples to aid in the detection of disease, whereas RALPH relates to the identification and confirmation of the biomarkers themselves. These two methods are not one in the same. Thus, RALPH is essentially nonanalogous art and should not be used as a basis

for rejection.

Indeed, the Office action itself highlights this point in its characterization of RALPH. For instance, the Office action characterizes RALPH as teaching:

> a method of identifying differentially expressed markers using RNA fingerprinting, and the techniques used by Ralph et al. include amplification of mRNA using random primers and identifying differentially expressed molecules using gel electrophoresis. Ralph et al. further explicitly teach that "frequently mRNAs identified by RNA fingerprinting or differential display as being differentially regulated turn out not to be so when examined by independent means. It is critical that the differential expression of all mRNAs identified by RNA fingerprinting ***be confirmed*** as such by an independent methodology." (see page 10 of Office action, emphasis added).

Unlike the instantly claimed invention, RALPH is concerned with the identification of new biomarker candidates by screening for differentially expressed mRNAs, followed by confirming or validating the identified biomarkers. By contrast, the present invention is directed to the detection of disease biomarkers in RNA samples, rather than, as with RALPH, confirming or validating a biomarker that has already been identified.

Because the instant claims are not drawn to a method of confirming already identified biomarkers, but instead are drawn to a method of identifying biomarkers useful for detecting diabetes, RALPH does nothing to remedy the failure of PAGE and SHARMA to render the invention obvious.

In light of the above remarks, Applicant respectfully requests reconsideration and withdrawal of the instant Section 103 rejections.

Claims 10 and 17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Sreekumar *et al.* (Diabetes (2002) 51:1913-1920) ("SREEKUMAR") in view of Affymetrix GeneChip Human Genome U133 Set Information sheet (2001) ("AFFYMETRIX"), and also in view of SHARMA

Applicant respectfully traverses. The Office action first asserts that it would have been obvious to one of skill at the time the invention was made to have modified the teachings of SREEKAMUR so as to have used the U133 microarray set taught by AFFYMETRIX for the expected benefit of assaying more genes in the assay. Applicant agrees that this motivation may be applicable to the method taught by SREEKAMUR which teaches methods of looking for differential expression of transcripts encoded by genes on Hu6800 arrays in ***skeletal muscle*** of diabetic patients and healthy control subjects. However, the instant claims are drawn to a method of identifying a marker expressed in ***blood*** useful for detecting diabetes, and therefore this motivation is not applicable to the methods instantly claimed.

The Office action further asserts that "it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods of SREEKAMUR (which teaches methods of looking for differential expression of transcripts encoded by genes on Hu6800 arrays in muscle of diabetic patients and control subjects) "in view of Affymetrix" (teaching of a human genome U133 microarray set useful for monitoring the relative mRNA abundance of several human genes including the DZIP gene) "so as to have additionally tested the blood of the subjects having diabetes and control samples and in particular to have completed this testing on total blood RNA." The Office action asserts that one "would have been so motivated by the express teachings of Sharma *et al.* that disease exerts a global effect on individuals and that this effect can be measured by gene expression in the blood." However, as discussed above, Applicant notes that SHARMA provides no exemplification of this express teaching. Not only does SHARMA ***not teach that diabetes is a disease which can be identified using markers which are differentially expressed in blood***, as required by the instant claims, SHARMA does not teach or exemplify methods of detecting differential

expression in blood of RNA encoded by disclosing even a single marker of a discrete mammalian gene differentially expressed for even one disease. In contrast, SHARMA discloses a ***non-prophetic working example*** of identifying biomarkers for a disease found in ***plants***. Accordingly, Applicant contends that the neither the prophetic nor the non-prophetic working examples of SHARMA does not provide motivation for one of skill reading SHARMA's WO document to modify the methods of SREEKAMUR by substituting blood for muscle as the location to identify markers useful in identifying diabetes.

The Office action further asserts that "the combined method necessarily would have resulted in determining a difference in expression in DZIP1 between healthy control and test samples, and so, in view of these teachings, the claimed invention is prima facie obvious", page 12 of the office action. Applicant respectfully traverses, and suggests that this may be a hindsight reconstruction, given that no art has been cited which teaches a difference in expression in DZIP1 between healthy control and test samples. As discussed above, one guideline published by the USPTO for determining obviousness after KSR (Federal Register, Vol. 72, No. 195; October 10, 2007) is simple substitution of one known element for another to *obtain predictable results.* As discussed above, SHARMA's prophetic examples do not provide a reliable scientific basis for practicing the claimed methods of identifying biomarkers useful in detecting diabetes in blood with a reasonable expectation of success. Thus, it would not have been predictable based on the cited art to one of skill in the art at the time the invention was made, who was considering combining the methods of PAGE with SHARMA by substituting blood for skeletal muscle as the tissue upon which to apply the claimed methods to identify markers useful in detecting diabetes, that such a combined method would be successful and/or predictably arrive at the claimed invention. In the absence of predictability in arriving at the claimed invention by substituting

blood for skeletal muscles in the methods of SREEKAMUR, one of skill would not have had a reasonable expectation of success in practicing the claimed invention, and thus no prima facie case of obviousness can be made.

Request for abeyance of obviousness-type double patenting rejections

Claims 1-9, 12-15, 19-20, 25-26, 28, 30-32, 37 and 54-63 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17-19-21, 23-24, 28-29, 33-34, 38, 41, 43, 49, 56, 57, 58 and 59 of copending application 10/601,518.

Claims 1-9, 12-15, 19-20, 25-26, 28, 30-32, 37 and 54-63 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 52, 53, 56, 57, 59, 61, 65, 66, 67, 68, and 69 of copending application 10/268,730 in view of PAGE.

Applicant respectfully request that the obviousness-type double patenting rejection be held in abeyance until there is an indication of allowable subject matter. Applicant will consider filing a terminal declaration upon the indication of allowable subject material.

CONCLUSION

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Dated: July 25, 2008

Respectfully submitted,

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